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PEER REVIEWED

Revisiting Ethics and Human Subject Safety in Clinical Research

Maribelle Guloy, MSHS, CCRP

Academic institutions have, on occasion, been found to be in gross violation of the norms for ethical conduct of clinical research by subjecting human volunteers to experiments involving untoward risks to their safety and lives. Similarly, pharmaceutical companies have sometimes demonstrated a lack of ethical sensitivity when pursuing clinical trials in resource-poor countries. Together, these historical events suggest that clinical research should be conducted based on careful and sensitive practices following the ethical principles and regulations highlighted in the following sections.

Part I: Ethics and Federal Regulations

Basic Principles of the Belmont Report

Since its release in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the U.S. government's volume on "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" (otherwise known as the Belmont Report) has outlined the guiding principles for the treatment of volunteers in clinical research.{1} It is the cornerstone statement of ethical principles, such as "respect for persons," "beneficence," and "justice," upon which the federal regulations for the protections of subjects are based.

The principle of respect for persons requires that each person has the right to autonomy and

that those with diminished autonomy should be protected. Therefore, the ethical guidelines must be clear about providing extensive protection to individuals who cannot self-determine.

A requirement of the principle of beneficence is that clinical research should be conducted with the safety of the human subjects as the primary interest.

A mandate of the principle of justice is that research involving human subjects needs to demonstrate fairness. Fairness means that individuals participating in clinical research are likely to benefit from the results or the applications of the research.

These ethical principles are fundamental for understanding the cross-cultural applicability in the era of globalization of research.{2} An issue for the global community, particularly in the low-income countries, would be the acceptability of the ethical principles developed in regions of the world with different standards of healthcare.

The Common Rule

Applicable federal regulations concerning clinical research have been derived from the ethical principles described in the Belmont Report. The regulations governing human subject research collected in the "Federal Policy for the Protection of Human Subjects" (otherwise known as the Common Rule) by the U.S. Department of Health and Human Services{3} apply to studies supported by federal agencies. These regulations establish the main protective mechanisms for safeguarding the rights and welfare of human research subjects.{4}

Review by an Institutional Review Board

Clinical research institutions are required to protect the rights, safety, and welfare of the research participants under the authority of the U.S. Food and Drug Administration (FDA).{5} An institutional review board (IRB) operating in compliance with federal regulations for human subject protection must be in place.{6} Subject to the FDA's IRB regulations, IRBs conduct ethical, administrative, and scientific peer reviews of FDA-regulated products.{7}

Summary

The ethics of clinical research and federal regulations have evolved over the past 60-plus years. As the cornerstone of ethical principles, the Belmont Report should remain relevant today. Compliance with these ethical principles and federal regulations provides assurance that the rights, safety, and welfare of research participants are protected.

Part II: Review of Literature

Nature of the Problem

Society's perception of research involving human subjects is shaped by the way this research is conducted by the pharmaceutical and medical device industry, clinical research organizations, medical and academic institutions, investigators, and other clinical research professionals.

Since very early in the history of medical research, violations of the rights of human subjects have been documented.{8} For example, a long-term U.S. study of untreated syphilis in the Black male population was conducted by the government without informed consent or a certainty of treatment; disabled elderly patients who were not capable of giving consent to a study at the Brooklyn Jewish Chronic Disease Hospital were injected with live cancer cells; and mentally retarded children at the Willowbrook State School in Staten Island, N.Y. were deliberately infected with hepatitis C virus.

Beyond the pillars of ethical conduct of clinical research lies the responsibility of researchers at academic medical centers and in the pharmaceutical and medical device industry to design and conduct clinical trials with consideration for the protection of human subjects. Additional ethical principles should be applied for clinical trials conducted outside the United States—particularly in resource-poor settings.

Part III: Principles of Ethical Clinical Research Conduct

Social and Clinical Value

The fundamental principle of clinical research resides in the value the study has for

society.{9} However, there is ambiguity in defining social value and who decides the constitution of social value with respect to research involving human subjects. Clinical research cannot ensue without the participation of human volunteers who submit to medical experimentations, which may involve risks to their safety and lives.{1}

Nevertheless, in late-phase trials, the potential for benefit to future patients as well as the generalizable knowledge produced in the experimentation can be anticipated. Clinical research ethicists argue that the anticipated clinical value of the intervention justifies the risks involved in the experimentation. Further, they posit that social value resides in the knowledge accrued as part of the experimentation and the anticipated clinical value to future patients.{9} While clinical research offers no promise of direct therapeutic benefit to the participants, the experimentation should be justified in relation to social and clinical value.{10}

Scientific Validity

Clinical research must be designed in conformity with valid scientific principles to produce relevant results.{11} Fair subject selection is also required to ensure that the efficacy and adverse effects of the intervention are being tested in the general population, rather than a subset of the population.{12} The research question, study design, methodology, and statistical plan must be carefully considered with respect to scientific validity and relevance.{13} A systematic evaluation of the different aspects of clinical research should be ascertained by the scientific, local research, or independent ethics committees before the launching of any clinical research conduct.{5}

Fair Subject Selection

Ethical research involves promoting respect for all human beings and protecting their rights and welfare. Subject selection should be done on the basis of scientific importance, not on convenience, vulnerability, or bias.{14} Vulnerable individuals, whose decisional capacity might be limited or restrained based on impaired cognitive skills, unfavorable social, or economic condition, should not be targeted for research participation.{8} Therefore, only those prospective human subjects who meet the research criteria and voluntarily submit for

participation should have an equal chance for selection to participate in the study.{11}

Informed Consent

Informed consent is one of the most important aspects of clinical research ethics. The requirement of an informed consent is designed to protect the rights of human subjects, and such rights should be treated above and beyond the interests of science.{14} Autonomy is an essential element of the consent process to ensure human subject protection; it refers to the subject having autonomy of thought, intention, and action when making decisions about participating in clinical research.

The study information disclosure should be aimed at enabling the subject to understand the clinical research process, the risks and benefits associated with clinical research procedures and the intervention, and the likelihood of success. Under the federal regulations, approval by a competent ethics committee or IRB of an informed consent is necessary before it can be executed in clinical research.{5}

Part IV: Important Concepts and Issues

Minimal Risk

The term "risk" in the human subject protection regulations refers to minimal risks—defined as being such that the probability of harm or injury, such as physical, psychological, social, or economic, occurring from research participation is not greater than that for a person involved in the context of going about their ordinary life or undergoing routine medical tests.{15} Following established professional and scientific standards, IRBs should adopt procedures to avoid the possibility of applying subjectivity leading to overestimation or underestimation of harm.{14}

Undue Influence, Coercion, and Exploitation

Payment to research subjects may be construed as undue influence if it constitutes an amount sufficient to induce an individual who would otherwise not participate in a clinical research study.{12} It raises ethical concerns when it influences individuals by distorting their

perception of risks and benefits.{11}

Coercion is best exemplified in the exploitation of prisoners in clinical research because the incarcerated may be at greater risk for true coercion.{16} Additionally, the prison can be a convenient place to conduct research because of easy accessibility to research participants and the convenience of doing research in a controlled environment. Nevertheless, others view the exclusion of prisoners from clinical research equally unjust, particularly if the research study can improve the care of prisoners.{17}

Prisoners should not be excluded from research participation in the guise of human subject protection, but this view should not be interpreted without following the ethical rules and regulatory guidelines for medical research.{16} In the absence of coercion or undue influence, and if the risk-benefit ratio is justifiable, it may seem unjust to exclude prisoners from an opportunity for improved care. Nevertheless, given the wide range of prisoner abuses in the past, it is critical that the clinical research community should exercise greater care in any research conducted in settings involving incarceration.{17}

Data Integrity

The data lifecycle covers the period from data acquisition to interpretation, reporting, and archiving. Any violation of data integrity brings harmful effects, as it could pave a way for deadly treatments to reach the market, and manifestations of the problem range from falsification and fraud to poor data management.

History is rife with disaster stories related to poor data tracking after an investigational treatment has been dispensed.{18} However, these events led to the development of research regulations and changes in the drug evaluation process. As per Good Clinical Practice guidelines, validation should be conducted to ensure data completeness, accuracy, reliability, and consistency.{19} Professionals in the industry responsible for data reporting and evaluation must ensure that the data are sufficient, valid, and of highest quality.

Conflict of Interest

Investigators with financial interests in companies sponsoring their clinical research studies could create a condition in which their professional judgment may be impaired, favoring their financial interests over the welfare of their patients.{20} As per regulatory guidelines and ethical research, professional judgment regarding the welfare of patients or the validity of research should not be influenced by a secondary interest, such as financial gain.

Scientific interests may also create a condition for conflict. Reported cases of conflict of interest continue to exist, and underscore the need for more ethical oversight to promote transparency and accountability in clinical research.{8} The research community must be vigilant to prevent any potential conflict of interest from arising, and research institutions should create effective and ethical conflict of interest policies to safeguard research quality and trust.{21}

Part V: Special Ethical Concerns in Clinical Research

Research in Resource-Poor Settings

When western pharmaceutical and biotechnology companies conduct research in resource-poor countries, questions arise about which research practice standards should govern the studies.{22} Economic conditions and local cultural traits can influence how these standards are applied.

A critical issue, mainly for low- and middle-income countries (LMICs), is the potential for exploitation. The majority of the population in an LMIC will not have the same resources as those from western countries in terms of health access and affordability.

Clinical research may offer human subjects some benefits of short-term access to care. It may also help build the infrastructure for healthcare and increase research and healthcare capacity. Nevertheless, a requirement of research in LMICs is that it must address the aforementioned questions about rights or justice.

Western pharmaceutical and biotechnology companies should think about whether healthcare

economic goals alone constitute suitable reasons to conduct research in an LMIC.{22} To avoid exploitation of an LMIC's population, the research should be relevant to the health needs of the country, better care should be provided, and responsibilities owed to human subjects should be considered.

Another critical issue in conducting clinical research in LMICs is the validity of the consent process.{23} While western standards promote autonomy, some foreign countries view consent as a collective decision-making process.{24} In LMICs in which a subset of the population may be illiterate, or when a tribal chief or elder is traditionally involved in making medical or research decisions, voluntary and fully informed consent may be an issue.

Simply put, the issues surrounding the conduct of clinical research in LMICs can be difficult and challenging, in terms of understanding and knowing which monitoring standards and ethical guidelines to enforce.{22}

The Use of Placebo

There are compelling reasons for the use of placebo in clinical trials, and one notable scenario is when there is no effective treatment available for the condition being studied.{25} The use of placebo is permitted by ethical guidelines when no effective treatment exists, when withholding treatment poses risks, or when compelling methodological reasons are allowed for the use of placebo.{26}

Nevertheless, from an ethics and science standpoint, many consider placebo as contrary to the interests of the subjects, and therefore, not ethical. That view is justified by the argument that when effective treatment exists, the use of placebo is unacceptable.{23}

The relevant question for many is not whether the investigational drug is better than placebo, but whether it is better than standard treatment. Viewed in this light, active treatment controls are because no subject goes without treatment. However, the use of placebo is permissible and ethically acceptable, as it allows researchers to determine whether the effects of a test drug are real or a result of the placebo effect.{25}

Conclusion

Revisiting ethics in clinical research serves to remind the research community about the ethical violations that have occurred in the past. It also serves to enforce the ethical principles and regulatory guidelines that have evolved to protect the rights and safety of human subjects.

Knowledge of the ethical and regulatory aspects of clinical research is essential for all clinical research professionals. Biomedical researchers and other research professionals in the academic community and in the pharmaceutical and device industry have the responsibility to design and conduct clinical trials—in any setting—that make consideration for the protection of human subjects a paramount concern.

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Maribelle Guloy, MSHS, CCRP, (guloymaribelle@gmail.com) is Director of Clinical Operations at HBT Labs, Inc. in Brea, Calif. This article is based on work she did as part of her doctoral program requirements while studying at Nova Southeastern University, from which she will receive her Doctor of Health Science degree with a concentration in global health in early 2019.

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PEER REVIEWED

A Survey on Including Risks in the New "Key Information" Section of an Informed Consent Form

Katelyn Le, MS; Stacy Kopka, MS; Doreen Chaitt, RN, MPH; Jerome Pierson, RPh, PhD; Martha Nason, PhD; Tracey Miller, RN, CCRP

[*Note: Since the writing of this article, the Secretary's Advisory Committee on Human Research Protections (SACHRP) of the U.S. Department of Health and Human Services has released recommendations on writing Key Information. The recommendations can be found online at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-c-november-13-2018/index.html.*]

Informed consent forms (ICFs) are growing longer and more complex.{1–4} The forces behind this trend may be well-intentioned, such as the desire to disclose more accurate and complete information{1}; however, it raises questions about whether important information is buried in lengthy documents, as well as whether ICFs can be structured to better emphasize the information that is most relevant to a study participant.

Recent updates to what is generally known as the Common Rule for protection of human subjects in research are in part meant to respond to this trend. Among these updates is the introduction of a new section called "Key Information"—every ICF now must open with the

most important information that potential subjects would want to know when deciding to join a study. But what exactly should this new section contain?

This question is crucial to us, a group of writers and reviewers who work with investigators to develop ICFs (the program was described in a 2013 issue of the ACRP *Monitor*{5}). For groups like ours, it is important to explore how best to implement the new regulations in a way that promotes consistency across different ICFs.

As an initial step, we wanted to understand how to objectively decide which risks to provide as Key Information. A survey was conducted to investigate how institutional review board (IRB) members, medical monitors, and principal investigators (PIs) view which risks should be considered Key Information. The hypothesis was that cohorts would have differing viewpoints on selecting these risks.

While the findings of this exploratory study demonstrate variability in viewpoints, they also suggest a number of points of consensus to consider when writing Key Information.

A Refresher on Key Information

The Revised Common Rule was issued by the U.S. Department of Health and Human Services in January 2017 and is set to go into effect January 2019. It updates the original 1991 Common Rule regulations to address various issues in modern human subjects research, such as the trend toward longer, more complex ICFs. The addition of the new Key Information section is one such change meant to "combat the growth in length and complexity" of ICFs and stop important information from being "buried."{6}

As described in the Revised Rule, the consent should give the "information that a reasonable person would want to have in order to make an informed decision" (Title 45 CFR Part 46.116(a)(4) in the *Code of Federal Regulations*). To do this, ICFs now "must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject […] in understanding the reasons why one might or might not want to participate in the research" (part 46.116(a)(5)(i)).

The Rule's preamble (XIV.A.4) suggests that this section may generally include the following information:

1. "the fact that consent is being sought for research and that participation is voluntary;
2. the purposes of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research;
3. the reasonably foreseeable risks or discomforts to the prospective subject;
4. the benefits to the prospective subject or to others that may reasonably be expected from the research; and
5. appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the prospective subject."

Identifying the Most Important Risks

It has been suggested that descriptions of study-related risks and discomforts are one particularly significant factor in bulking up ICFs,{1} and risks will likely pose similar challenges to writing "concise and focused" Key Information sections. The regulation provides flexibility in exactly what information to include; the preamble suggests including the "most important risks," like what a doctor might tell a patient in the clinical context with an emphasis on how those risks are changed in a research study (XIV.A.4). The language gives only a rough idea of the length of the "concise and focused presentation."

Although such language gives flexibility to individual projects, it challenges efforts to consistently implement the rule across multiple projects. The subjectivity of this language may make it difficult to reach a consensus on which risks to include in Key Information. In the absence of specific guidance on writing Key Information, a survey was designed to explore outstanding questions about including risks in this new section.

A Survey on Risks in Key Information

A digital survey tool was created using a PDF form and disseminated and returned via e-mail. The survey opened with a brief introduction to the Revised Common Rule and the new Key Information section. Next, the survey presented a four-page ICF Potential Risks section, which

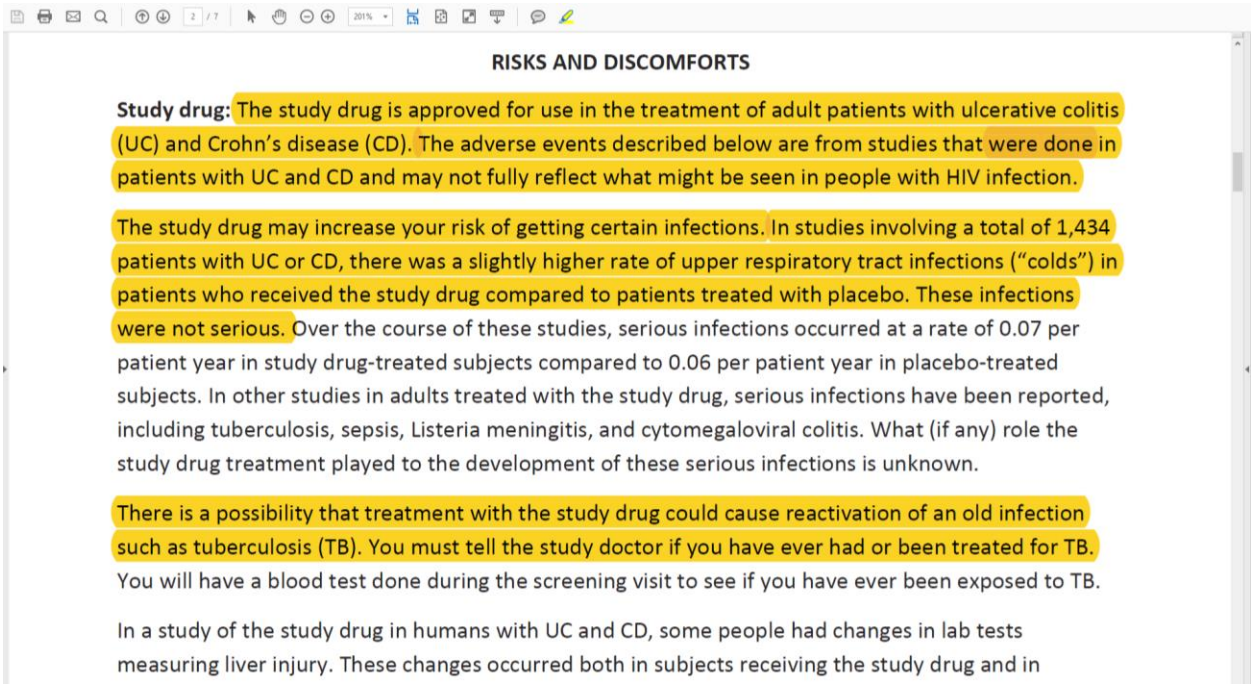
included 39 discrete risk ideas, from an IRB-approved ICF for a Phase I study of a licensed monoclonal antibody in HIV patients.

This ICF language was chosen because it is representative of studies at our institute (early-phase trials of investigational agents), and includes a variety of risks to differentiate characteristics such as frequency, seriousness, and certainty. Additionally, the survey included IRB-approved risk language for select standard (non-experimental) study procedures: bone marrow biopsy, apheresis, and venipuncture.

Respondents were asked to review the sample ICF Potential Risks section and use the digital highlighter tool in a PDF viewing program to mark the risk ideas that they would move to Key Information (see Figure 1). Respondents were instructed to focus on risk ideas, not exact wording, with the understanding that language would in practice be revised to fit into a standalone Key Information section.

An open-ended question asked respondents to explain what factors influenced their decisions in selecting key risks. Also, the survey included multiple choice demographic questions.

Figure 1: Excerpt from a Completed Survey



RISKS AND DISCOMFORTS

Study drug: The study drug is approved for use in the treatment of adult patients with ulcerative colitis (UC) and Crohn's disease (CD). The adverse events described below are from studies that were done in patients with UC and CD and may not fully reflect what might be seen in people with HIV infection.

The study drug may increase your risk of getting certain infections. In studies involving a total of 1,434 patients with UC or CD, there was a slightly higher rate of upper respiratory tract infections ("colds") in patients who received the study drug compared to patients treated with placebo. These infections were not serious. Over the course of these studies, serious infections occurred at a rate of 0.07 per patient year in study drug-treated subjects compared to 0.06 per patient year in placebo-treated subjects. In other studies in adults treated with the study drug, serious infections have been reported, including tuberculosis, sepsis, Listeria meningitis, and cytomegaloviral colitis. What (if any) role the study drug treatment played to the development of these serious infections is unknown.

There is a possibility that treatment with the study drug could cause reactivation of an old infection such as tuberculosis (TB). You must tell the study doctor if you have ever had or been treated for TB. You will have a blood test done during the screening visit to see if you have ever been exposed to TB.

In a study of the study drug in humans with UC and CD, some people had changes in lab tests measuring liver injury. These changes occurred both in subjects receiving the study drug and in

Respondents used the highlighter tool in a PDF-reading program to identify the risks they would move to the new Key Information section. Text that was not highlighted would remain in the main Risks and Discomforts section of the ICF.

To capture the viewpoints of a variety of stakeholders in human subjects research at our institute, the survey was distributed to three cohorts: all primary IRB members (n: 9), all medical monitors (n: 3), and a convenience sample of PIs (n: 17, N: 29). There were nine responses (response rate: 31%). Respondent demographics are presented in Table 1.

Table 1: Survey Respondent Demographics (N=9, response rate=31%)

Role	Medical monitor	3
	PI	1
	IRB member	5
Time in Research	< 5 years	1
	5–10 years	1
	11–20 years	3
	> 20 years	4
Age	40–49 years	3
	50–59 years	2
	60–69 years	4
Sex	Male	4
	Female	5

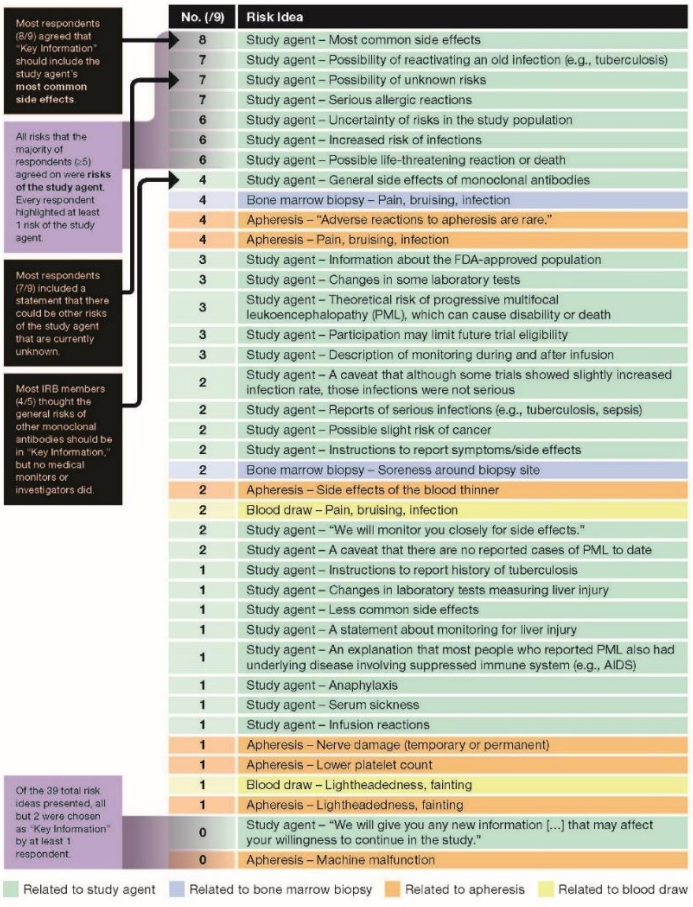
An honest broker deidentified responses before analysis. The surveys were then analyzed by counting and categorizing the risks addressed in the highlighted text.

What Did Respondents Consider Key?

Out of the 39 total risk ideas, there were only seven that most respondents (more than half) agreed to include; all seven were related to the study agent (see Figure 2).

Every respondent highlighted at least one risk of the study agent. The seven risk ideas that most respondents highlighted were the study agent's most common side effects, most serious known risks, risks that are important to the study population, and the possibility of unknown study agent risks. Interestingly, this last risk idea is not a specific "most important risk," but rather a disclosure of theoretical risk. Perhaps respondents felt it important to include as a "reasonably foreseeable risk" an acknowledgement that the study agent is experimental and not all risks can be foreseen.

Figure 2: Respondents Who Thought Each Risk Idea in the Sample ICF Should be Moved to the New Key Information Section



All but one of the IRB members thought the general risks of monoclonal antibodies as a class should be in Key Information, but no medical monitors or PIs did (see Figure 2).

The survey population was not large enough to compare subgroups, so we cannot conclude that there is a significant difference in viewpoints between IRB members and other groups. This finding does, however, support the initial hypothesis that people in different roles in human subjects research will have differing interpretations of Key Information, which is not surprising since one would expect each cohort to review the consent with a different purpose in mind.

Nevertheless, possibly due to the small sample size, this was the only risk idea for which there was a clear difference in response between cohorts. For many of the other 38 risk ideas, individual responses were too variable to identify trends within cohorts. Conceivably, studying a larger population could help identify cohort-specific preferences, but it is also possible that individuals within a single cohort have such differing perspectives that it is impossible to identify trends about what should comprise Key Information.

Of the 39 total risk ideas presented, all but two were chosen as Key Information by at least one respondent (see Figure 2).

This means that almost 95% of the risk ideas in the sample ICF were chosen by at least one respondent. Thus, respondents together thought most of the study risks should be included in Key Information. This may support an argument for considering all study risks as "most important" for a potential subject's decision.

Of the 39 total risk ideas, each respondent chose an average of 12 risks (range 6 to 19).

Interestingly, the highest and lowest numbers of chosen risk ideas were both from IRB members. These numbers are the result of an artificial task, since respondents were only asked to highlight risks they would move to Key Information, not to write the actual Key Information section. However, differing interpretations of the regulation's language (for example "concise and focused presentation" of "most important" information) do not define how short this section should be. The Revised Common Rule's preamble does mention that length may depend on the length of the entire ICF, with longer ICFs having longer Key Information.

What Guided Respondents' Decisions?

When asked what factors influenced their decisions, most respondents mentioned that they considered the severity/seriousness and frequency of the risks. Other factors respondents mentioned were complexity, certainty, and the study population.

Complexity was one topic with divergent implications. For example, one respondent indicated an intention to avoid complexity in Key Information and reserve complex ideas for the main body of the consent ("big concepts [first]…details later"); however, a different respondent preferred to use the Key Information section to address the most complex issues (things anticipated to take the "most time to explain or subjects would most want to know/talk about").

Also, multiple respondents included discussions of why they did or did not include risks of procedures. Two respondents said that they would include study procedure risks to essentially "kill two birds with one stone"—first to highlight the types of study procedures required on the study and secondly to mention the risks. From these reactions, it appears that when writing Key Information sections, it will most likely be necessary to introduce and briefly explain the study procedures before presenting the risks of those procedures.

Writing Key Information

These findings highlight the variability in viewpoints of research professionals, both between and within cohorts, on selecting risks as Key Information in the absence of more specific guidance. The Revised Common Rule's language was meant to lend flexibility to the specific contexts of a given study. For example, the content of Key Information will likely differ between Phase I and Phase III studies, since a Phase III study would have more risk information to reference, would be focused primarily on efficacy rather than safety, and in some cases may involve a different study population (e.g., patients versus healthy volunteers).

However, this regulation introduces more subjectivity—and perhaps even bias—into the process of identifying the "most important" risks. Additional official guidance may help minimize variability and facilitate the consistent writing of this new section.

In some situations, a discrete, standalone Key Information section may not be needed. The preamble to the Revised Common Rule acknowledges that institutions may determine that, for simple studies with short ICFs, the requirement for Key Information may be fulfilled by arranging the content so that the "most important" information (such as the required elements of consent) come first, followed by other language and disclosures less relevant to decisions about participation.

This simple solution would avoid repeating content and making broad judgments about which information will be most important to participants. Conversely, in longer ICFs for more complex studies, information would be summarized upfront in Key Information and then provided in greater detail later in the document. For studies with long lists of possible risks, this may mean concisely presenting the most common and severe risks upfront, followed by a comprehensive description of all reasonably foreseeable risks later in the ICF.

In situations where a standalone Key Information section is warranted, the results of this survey suggest considering the following points:

- Focus on the risks of the study agent (or other investigational procedure).
- Mention the possibility of unknown risks in the population being studied.
- Include the risks that are the most frequent and/or serious.
- Anticipate variability in this section based on the protocol specifications (for example, study population, phase, prospect for benefit, treatment alternatives) and the perspectives of reviewers.

Conclusion

This survey was exploratory and limited in nature. It used a small sample at a single institution and, though the overall response rate was within the expected range for electronic surveys,{7–10} the cohort response for PIs was lower than expected (6%).

Respondents could only consider the information provided, which excluded other ICF sections and study documents that may also have affected choices about the content of the Key Information section. In addition to risks, there may be other factors that a "reasonable person"

would find important when deciding to participate, which may affect the length and scope at which risks are discussed upfront.

In the future, the authors of this survey plan to design a larger survey examining risks and the Key Information section in a broader population including research subjects.

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Katelyn Le, MS, (katelyn.le@nih.gov) is a medical writer with the Clinical Monitoring Research Program Directorate of the Frederick National Laboratory for Cancer Research, sponsored by the National Cancer Institute in Rockville, Md.

Stacy Kopka, MS, is a medical writer manager with the Clinical Monitoring Research Program Directorate of the Frederick National Laboratory for Cancer Research, sponsored by the National Cancer Institute.

Doreen Chaitt, RN, MPH, is director of the IRB Office and deputy director with the Office of Clinical Research Policy and Regulatory Operations, Division of Clinical Research, at the National Institute of Allergy and Infectious Diseases.

Jerome Pierson, RPh, PhD, is director of the Office of Clinical Research Policy and Regulatory Operations, Division of Clinical Research, at the National Institute of Allergy and Infectious Diseases.

Martha Nason, PhD, is a mathematical statistician with the Biostatistics Research Branch, Division of Clinical Research, at the National Institute of Allergy and Infectious Diseases.

Tracey Miller, RN, CCRP, is a protocol navigation manager with the Clinical Monitoring Research Program Directorate of the Frederick National Laboratory for Cancer Research, sponsored by the National Cancer Institute.

DECEMBER 2018 CLINICAL RESEARCHER

HOME STUDY

Ethics in Action

Revisiting Ethics and Human Subject Safety in Clinical Research

LEARNING OBJECTIVE

After reading this article, the participant should be able to summarize the content and significance of the Belmont Report and the Common Rule, explain the function of an institutional review board in conducting clinical research, and explain the impact of scientific validity, fair subject selection, and informed consent on the conduct of clinical research.

DISCLOSURE

Maribelle Guloy, MSHS, CCRP: *Nothing to disclose*

1. The ethical principles of respect for persons, beneficence, and justice are described in:
a) The Belmont Report
b) The Common Rule
c) *The Code of Federal Regulations*
d) The Constitution of the United States

2. The principle that requires that each person has the right to autonomy and that those with diminished autonomy should be protected is:
a) Respect for persons
b) Beneficence
c) Justice
d) Scientific integrity

3. The principle that requires that clinical research be conducted with the safety of human subjects as the primary interest is:
a) Respect for persons
b) Beneficence
c) Justice
d) Scientific integrity

4. The principle that mandates that research involving human subjects needs to demonstrate fairness is:

a) Respect for persons
b) Beneficence
c) Justice
d) Scientific integrity

5. The "Federal Policy for the Protection of Human Subjects" is otherwise known as:

a) The Belmont Report
b) The Common Rule
c) The Tuskegee Report
d) *The Code of Federal Regulations*

6. In order to promote respect for all human beings and protect their rights, subject selection should be done on the basis of:

a) Vulnerability
b) Bias
c) Convenience
d) Scientific importance

7. A requirement of clinical research that is designed to protect the rights of human subjects and to ensure that those rights should be treated above and beyond the interests of science is:

a) Social and clinical value
b) Scientific validity
c) Fair subject selection
d) Informed consent

8. If payment to research subjects constitutes an amount sufficient to induce an individual who would otherwise not participate in a clinical research to participate, it may be construed as:

a) Undue influence
b) Coercion
c) Exploitation
d) Unfair subject selection

9. The data lifecycle covers the period from data acquisition through:

a) Review
b) Interpretation
c) Reporting
d) Archiving

10. The use of a placebo is permitted by ethical guidelines when:

a) There are financial constraints on the use of the experimental drug.
b) No effective treatment exists.
c) There is an excess of clinical trial participants.
d) The outcome of the clinical trial is already known.

A Survey on Including Risks in the New "Key Information" Section of an Informed Consent Form

LEARNING OBJECTIVE

After reading this article, participants will be able to describe the Common Rule and the intended purposes of the section on "Key Information" in informed consent forms.

DISCLOSURE

Katelyn Le, MS; Stacy Kopka, MS; Doreen Chaitt, RN, MPH; Jerome Pierson, RPh, PhD; Martha Nason, PhD; Tracey Miller, RN, CCRP: *Nothing to disclose*

11. Who introduced recommendations on writing Key Information in informed consent forms?
a) U.S. Department of Commerce
b) Institutional review boards
c) Office of Inspector General
d) Secretary's Advisory Committee on Human Research Protections

12. What has recently been updated to reflect similar recommendations to the ones released?
a) Informed consent forms
b) ICH-GCP E6 (R2)
c) The Common Rule
d) Patient information leaflets

13. Which of the following is an example of Key Information that would be included in an informed consent form?
a) Reasonably foreseeable risks or discomforts of the study to prospective subjects.
b) Assessments of the financial stability and long-term research goals of the study site.
c) Mandatory warnings associated with the participant's stated health habits and lifestyle trends.
d) Details of lawsuits related to investigational products similar to the one under current study.

14. When does the Revised Common Rule go into effect?
a) January 2017
b) December 2018
c) January 2019
d) January 2020

15. Informed consent forms must now start "with a concise and focused presentation on key information…to assist a prospective subject…." Which part of which regulation does this refer to?
a) 21 CFR Part 11
b) 45 CFR Part 46.116(a)(4)
c) 21 CFR Part 312
d) 45 CFR Part 46.116(a)(5)(i)

16. What did the survey described in this article open with?

a) A brief introduction to the Revised Common Rule and the new Key Information section.
b) The requirements for elements in informed consent forms as per ICH GCP E6(R2).
c) Guidelines for protection of human subjects in research.
d) Institutional review board requirements for obtaining consent.

17. How many cohorts was the survey distributed to?

a) Nine
b) Five
c) Three
d) Two

18. How many risks from a total of 39 did most survey respondents think should be included in Key Information?

a) Eleven
b) Seven
c) Five
d) Three

19. What did every survey respondent highlight to be included in the Key Information section?

a) Every known or suspected risk for the study population.
b) At least one risk of the study agent.
c) A listing of the visit schedule and procedures to be conducted.
d) The possibility that a participant might not receive the active product.

20. Respondents were asked what factors influenced their decision, and most of them said:

a) It depended on the individual's role in research.
b) It was based on the therapeutic area being investigated.
c) They reviewed previous studies that were conducted with this molecule.
d) They considered the severity/seriousness and frequency of the risks.